Risk Analysis, Vol. 19, No. 6, 1999

Ethylene Oxide Cancer Risk Assessment Based on Epidemiological Data: Application of Revised Regulatory Guidelines

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Ethylene oxide (EO) research has significantly increased since the 1980s, when regulatory risk assessments were last completed on the basis of the animal cancer chronic bioassays. In tandem with the new scientific understanding, there have been evolutionary changes in regulatory risk assessment guidelines, that encourage flexibility and greater use of scientific information. The results of an updated meta-analysis of the findings from 10 unique EO study cohorts from five countries, including nearly 33,000 workers, and over 800 cancers are presented, indicating that EO does not cause increased risk of cancers overall or of brain, stomach or pancreatic cancers. The findings for leukemia and non-Hodgkin's lymphoma (NHL) are inconclusive. Two studies with the requisite attributes of size, individual exposure estimates and follow up are the basis for dose-response modeling and added lifetime risk predictions under environmental and occupational exposure scenarios and a variety of plausible alternative assumptions. A point of departure analysis, with various margins of exposure, is also illustrated using human data. The two datasets produce remarkably similar leukemia added risk predictions, orders of magnitude lower than prior animal-based predictions under conservative, default assumptions, with risks on the order of 1×10^{-6} or lower for exposures in the low ppb range. Inconsistent results for "lymphoid" tumors, a non-standard grouping using histologic information from death certificates, are discussed. This assessment demonstrates the applicability of the current risk assessment paradigm to epidemiological data.

KEY WORDS: Ethylene oxide; risk assessment; epidemiology; cancer guidelines.

1. INTRODUCTION

Ethylene oxide (EO) is a major commodity chemical with production levels in the US of 7.2 billion lb.[1] EO is used primarily as a chemical intermediate in the production of ethylene glycol, non-ionic surfactants and other derivatives in smaller quantities. EO is a well known alkylating agent that has been shown to express genotoxic activity in both *in vitro* and *in vivo* systems.[2] While recognized as an animal carcinogen for nearly 20 years, EO's potential as a human carcinogen has not been established.[3-6] In 1994, the International Agency for Research on Cancer (IARC) classified EO as category 1, "Carcinogenic in Humans", based primarily upon sufficient evidence in animals and genotoxic considerations.[7]

EO cancer risk assessments conducted by OSHA and the EPA in the 1980s, by necessity, relied upon rodent chronic bioassays.[8-9] Since that time, epide-

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0272-4332/99/1200-1135$16.00/1

miological and mechanistic research related to EO has increased dramatically. At the time of the EPA and OSHA rodent-based risk assessments only three small-scale human studies were available.[10-12] Now there are 14 additional published cohort studies involving multiple manufacturing and sterilizer facilities from five different countries.[13-26]

In parallel with the increasing amount of EO-related scientific data, both EPA and OSHA have been revising their risk assessment guidelines to be both more flexible and more amenable to advancements in scientific understanding and risk assessment methodologies. A key feature of the proposed revised EPA Cancer Risk Assessment Guidelines is the attempt to develop a process that better utilizes available scientific information, thereby increasing the incentive for additional research that could improve estimates of risk.[27] The new hazard characterization process, for example, focuses on a more complete description of the evidence from all sources (i.e., animal, human and mechanistic) leading to a clearer understanding of what is known and what is uncertain. When available, the use of high quality human data is preferable to the use of rodent data in risk assessment.[27,28] Absent sufficient scientific understanding, uncertainty is handled by incorporating default assumptions into the risk assessment. OSHA also supports greater flexibility, the use of all scientific evidence, an increased reliance on human data and the use of default assumptions in the absence of data. The agencies differ in their approaches to dose-response assessment. The EPA proposes a "point of departure" (POD) approach, whereas OSHA prefers model extrapolation below the range of observable data.

The intent of guidelines is to provide a framework and operational principles without being overly prescriptive. This objective is less challenging when traditional data sources such as chronic bioassays provide the basis for risk assessment. However with mechanistic and epidemiological data there has been much less experience upon which to base policy decisions. The EO cancer risk assessment presented in this paper is in response to a call for more case studies illustrating the application of guidelines to data-rich chemicals. It focuses on hazard characterization and dose-response assessment. It represents one of the first attempts to use a POD approach with epidemiological data, complementing results utilizing low-dose extrapolation methods. The results are also contrasted with prior EO risk assessments based on rodent data.

2. HAZARD CHARACTERIZATION

2.1. Chronic Bioassays and Genetic Toxicity

EO has exhibited carcinogenic activity in both sexes in rodent inhalation studies. The effects included brain glioma, lung adenoma, mononuclear cell leukemia, lymphoma and peritoneal mesothelioma. These studies were completed over 10 years ago and are described more fully elsewhere.[7]

EO is genotoxic. Both *in vitro* and *in vivo* studies of EO have detected positive responses for a number of genetic endpoints, including point mutations, sister chromatid exchanges (SCEs), chromosomal aberrations, micronuclei, DNA adducts and hemoglobin adducts.[2,7] EPA's proposed guidelines appropriately advocate that nontumor data may be used to characterize the shape of the dose-response curve in the low-dose region.[27] A genetic risk assessment, building upon a pioneering EPA effort,[29,30] concluded that the mode of action for genetic risk would include reciprocal translocations, and also chromosomal alterations and point mutations.[31] On the basis of mechanistic considerations, it is likely that two or more independent DNA lesions are required for reciprocal translocations, whereas for point mutations, a linear extrapolation would be appropriate. Therefore, the shape of the dose-response curve in the low-dose region should be nonthreshold and somewhere between linear and quadratic. Such an approach would be consistent with the recognition in the Guidelines that for some chemicals, both linear and nonlinear procedures should be displayed to reflect the interplay of complex dose-response relationships.

New research and refined interpretations of genetic toxicity data have also addressed the assumption that such information is predictive of carcinogenicity.[32,33] For example, SCEs and certain adduct counts are indicators of recent EO exposure, not necessarily damage.

Chromosomal aberrations observed *in vitro* in peripheral lymphocytes of humans do not indicate lasting chromosomal alterations. In contrast to *in vitro* data, EO is not a potent mutagen *in vivo*. It is unlikely that one can show from *in vitro* experiments what amount of damage, induced over a period of time prior to taking a blood sample, would remain in the lymphocyte available to be converted into a lasting chromosomal alteration. If humans are treated with a very potent alkylating agent, the DNA damage is sufficiently repaired within 48 hours such that chromosomal damage is not evident.

An additional limitation of EO genetic toxicity studies conducted in humans is their limited sample size and consequent inability to rule out potential confounding effects with a reasonable degree of confidence. Furthermore, the existing population monitoring studies assume that *in vitro* observations from peripheral lymphocyte data are relevant to predict carcinogenic effects in unrelated target organs. These issues are discussed in greater detail by others.[34-37]

Because the human population monitoring data on EO for genotoxic effects do not measure what they are intended to measure—effects of past levels of exposure—and because the study designs are limited by small sample size and potential for confounding, greater reliance for evidence of carcinogenicity should be placed on long-term, well conducted occupational mortality studies.

2.2. Occupational Epidemiology

The first epidemiology study of EO exposed workers, a cluster investigation by Hogstedt *et al.*, was published in 1979.[10] This small cluster investigation and two other small cohort studies[11-12] were available by the time of the OSHA and EPA prior risk assessments. Since the original cluster report, the number, quality and size of the published literature on EO exposed workers have expanded to include 17 published studies, 10 unique cohorts of nearly 33,000 workers with more than 800 cancers (some incident cases but mostly deaths due to cancer) from five countries (Table I). These studies include workers from Sweden, Germany, Italy, the US and Great Britain involved in EO production, its use as an intermediate or as a sterilizing agent. Three of the studies also include women.[15,22,23] Two of the studies are updates of prior publications by different authors.[19,21] The Morgan *et al.*[12] study of Texaco production workers was updated by Divine *et al.*[19], and the Greenberg *et al.* study[20] of Union Carbide (UCC) production workers was updated by Teta *et al.*[21] The largest of these studies is the NIOSH study by Steenland *et al.* of 18,254 male and female workers in 14 plants sterilizing medical products and spices.[22] The study by Wong and Trent was a partial parallel analysis of the NIOSH study with one additional year of follow up (18,728 workers, 403 cancer deaths, 17.6 years average length of follow-up).[26] The NIOSH study has an average observation period of 16 years with approximately 4900 workers followed up for more than 20 years from first exposure. Two of the manufacturing plants have even longer average follow up periods, 25 years for the Dow workers and 27 years for the UCC workers.[21,25]

Workers from studies with longer follow up also typically experience higher levels of exposure, since current EO workplace levels are substantially lower than in the past. In the early years of EO production and use (1940s), levels averaged around 14 ppm and about 5–10 ppm in the 1950s.[10] The early peak ppm values, however, are known to have been much higher (exceeding the odor threshold, greater than about 400 ppm) than the estimated eight-hour time-weighted average (TWA8).[6] Spills and accidental over-exposures were common in the early years, as were medical visits for treatment of acute effects.[20] As recently as the late 1960s to the mid 1970s, levels in sterilant operations have been reported to be from 20–75 ppm.[10,16] In 1984, the permissable exposure

Table I. EO Epidemiology Studies

Author	Country	Workers	Cancers	Average duration	Average observation
Hogstedt[a]	Sweden	240	7	4–9	?
Hogstedt	Sweden	175	20	3–30	?
Hogstedt	Sweden	355	13	9–13	?
Hagmar	Sweden	2,170	40	?	11.6
Thiess[a]	Germany	602	12	11	14
Kiesselbach	Germany	2,658	68	9.6	15.5
Morgan[a]/Divine	U.S.	767	19	>20	?
Greenberg[a]/Teta	U.S.	1,896	110	5.4	27.2
Steenland	U.S.	18,254	343	4.9	16.1
Bisanti	Italy	1,971	43	~7	~9
Gardner	UK	2,876	85	?	?
Olsen	U.S.	1,361	75	5.7	24.5

[a] Excluded from meta-analysis.

limit in the workplace was lowered by OSHA from 50 ppm to 1 ppm TWA8.

A properly conducted meta-analysis can be a useful approach to synthesizing information for chemicals such as EO that have been the subject of many epidemiological cohort studies with numerous endpoints examined in each investigation.[38] The EO studies available as of 1993 were identified and examined by Shore *et al.* as part of a meta-analysis.[6] His review includes a descriptive summary of each study with a critique, tests of heterogeneity, summarization of overall findings and trends by intensity/frequency of exposure (low, intermediate, high), duration of exposure (1–4 years, 5–9 years, 10+ years) and time since first exposure (<10 years, 10–19 years, 20+ years), sometimes referred to as latency for the cancers of *a priori* interest (cancers of the pancreas, brain, stomach; leukemia; non-Hodgkins lymphoma (NHL)). The interpretation examined the potential for confounding in the manufacturing setting and variations in results due to different conditions of exposure.

In the present hazard characterization, the EO meta-analysis has been updated, using the same methodology and exclusions[10,11,12,20] as the Shore *et al.* meta-analysis, to include the two studies that have become available more recently, specifically, the 1997 publication by Olsen *et al.* of a Dow cohort and an update of the Hagmar *et al.* sterilant workers cohort.[17,25] The Dow study focused on workers manufacturing ethylene and propylene chlorohydrin while working in EO production units. Consistent with Shore *et al.*, the larger Wong and Trent study[26] was used for all analyses except the temporal tabulations in which the NIOSH study was used.

Not included is a small cancer incidence study by Norman *et al.*,[39] 1995, that focused on breast cancer in females, a type of cancer excluded from the Shore *et al.* meta-analysis as not being of *a priori* interest. The breast cancer results are included in our discussion of gender sensitivity. Norman *et al.* reported only selected data on other types of cancer, noting that there were no increases in cancer incidence over that expected for leukemia, brain, pancreas and no cases of NHL.

2.3. Results of Meta-analysis

A summary of the results of the updated meta-analysis is presented in Table II. There are 876 cancer deaths in the 10 unique cohort studies included in the meta-analysis, compared to an expected 928 deaths. The cancer meta-SMR (standardized for age, sex and calendar year) is 0.94 (95% CI: 0.85, 1.05). No overall cancer excess is suggested. For all six of the cancer endpoints of *a priori* interest, the SMRs do not differ statistically from 1.0. The CIs for brain cancer, stomach cancer and leukemia are adjusted (widened) for heterogeneity. The SMR for leukemia decreases to less than 1.0 when the Hogstedt study (the reason for the leukemia heterogeneity) is excluded. Figure 1 illustrates the discrepancy in leukemia results between Hogstedt and the other EO studies.

There are no statistically significant positive trends with duration, intensity or latency, with the exception of brain cancer. The trend with latency is based on only four studies which provided brain cancer data by time since first exposure. The meta-SMR for brain cancer (0.96) is not elevated, based on seven studies that reported results for this cause. It is highly likely that brain cancer mortality rates were not increased for the five studies not reporting results for this type of cancer and that the meta-SMR would be even smaller if these data were included. Although there is not a positive trend with latency for leukemia, there are more cases than expected in the longest latency category (14 observed vs. 7.9 expected). The meta-SMR for NHL is moderately increased (1.34) and of borderline statistical significance (95% CI: 0.96, 1.89), but there are no positive trends with duration, intensity or latency.

Additional insights into the carcinogenicity of EO are presented by Stayner *et al.* who conducted exposure-response statistical analyses of workers from the medical products/spice plants included in the NIOSH mortality study.[40] Four exposure metrics were defined (cumulative, duration, average and maximum) and examined using both stratified (SMR life table) and modeling (Cox proportional hazards) approaches. A non-standard grouping of lymphopoietic tissue cancers was used in which lymphocytic leukemia and NHL were combined into a category called "lymphoid" tumors.

The stratified analyses from the Stayner *et al.* paper did not indicate any positive trends between exposure and cancer (stomach, kidney, pancreas, brain, leukemia, NHL) for any of the exposure metrics. Using the regression model, with cumulative EO dose entered as a continuous variable, the authors reported: 1) a statistically significant association with "lymphoid" cancers, 2) a weaker nonstatistically significant association with NHL and leukemia and 3)

Table II. EO Meta-analysis SMRs[a] and Trends

Endpoint	Obs./Exp.[b]	Meta-SMR	95% CI	Duration	Intensity	Latency
All Cancer	876/928	0.94	(0.85, 1.05)[c]			
Pancreas	37/39	0.95	(0.69, 1.31)	No	No	No
Brain	25/26	0.96	(0.49, 1.91)[c]	No	No	Yes[d]
Stomach	59/48	1.23	(0.71, 2.13)[c]	No	No	No
Leukemia	35/32	1.08	(0.61, 1.93)[c]	No	No	No
w/o Hogstedt	30/32	0.95	(0.64, 1.35)			
Non-Hodgkins lymphoma	33/25	1.34	(0.96, 1.89)	No	No	No

[a] SMR = Standardized mortality ratio.
[b] Expected numbers rounded to the nearest whole number.
[c] Adjusted for heterogeneity.
[d] $p < 0.05$, based on four studies with latency data for brain cancer.

inverse relationships with stomach, kidney and brain cancers. There were no notable findings in the analyses for the other exposure metrics.

The authors discussed the impact of a few highly exposed cases in the regression approach. Exclusion of the one extreme case (1,356 ppm years EO exposure) resulted in a risk estimate for "lymphoid" tumors of similar magnitude, but it was no longer statistically significant. No explanation was offered for the inverse relationship between EO exposure and lymphopoietic cancers in women.

Results for the four studies that included women are contrasted for gender differences (Table III). The Gardner *et al.*[23] study did not present the data by gender groups but by occupational setting. Since most manufacturing workers were men and most hospital sterilant workers were female in this study, this grouping serves the purpose. The Hogstedt *et al.*[15]

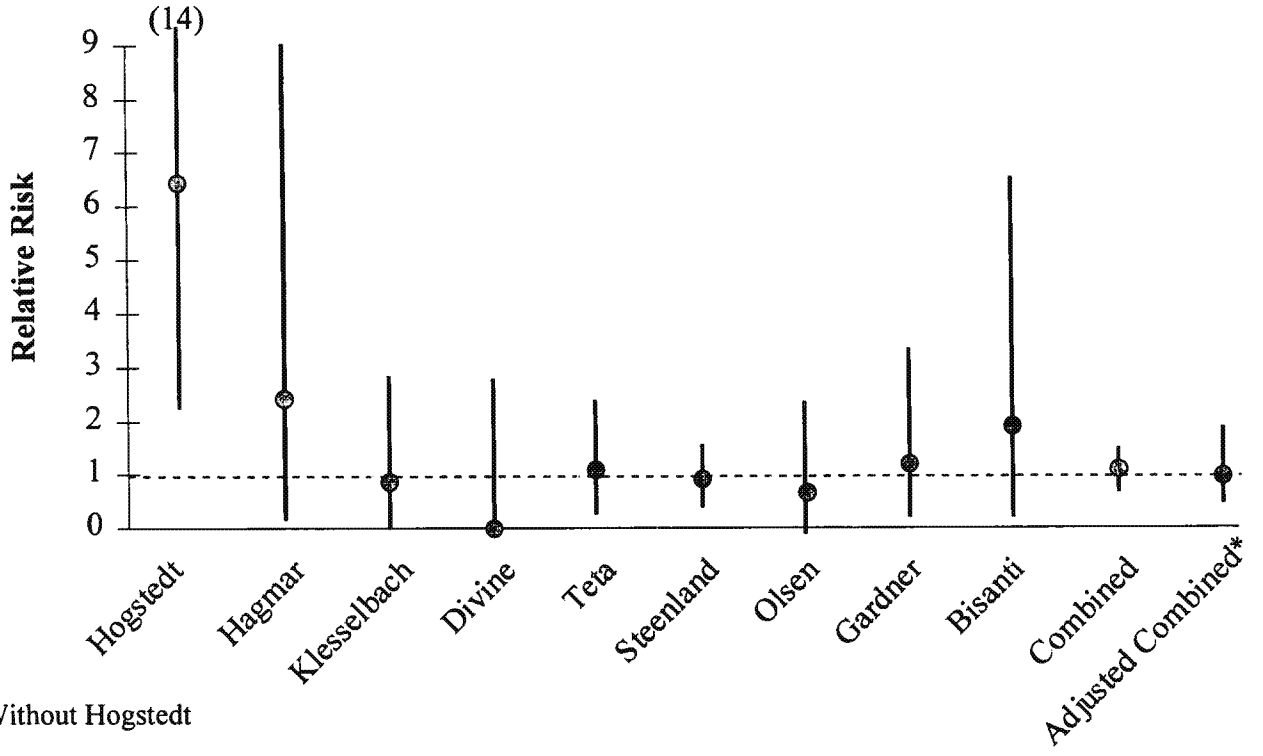


Fig. 1. Leukemia relative risks from EO epidemiology studies individually and combined.

study indicated leukemia excesses in both men and women; Norman *et al.*[39] reported no cases in men and one case in women, while the other two studies indicated lower rates of all cancer endpoints for women, particularly the Steenland *et al.*[22] study that included 10,040 women. This is one of two studies that reported data on breast cancer. The SMR is 0.85 with 42 observed and 50 expected deaths among women for this cause. Norman *et al.* reported an SMR of 1.7 (based on 12 incident cases) that diminished over time. The issue of early case-finding has been raised (artificially elevated observed rates due to earlier detection by medical screening).[41] These studies suggest that there is no apparent increased sensitivity for women.

2.4. Hazard Summary

Consistent with EPA's concept of providing narrative descriptions of the evidence related to carcinogenic hazard, the following characterizes the evidence for EO.

There is sufficient evidence that EO causes increased tumors at multiple sites in male and female rats and mice. The relevance of these findings to humans is uncertain because of the less than persuasive evidence of carcinogenicity in a large body of well conducted, long term studies of workers exposed to EO in the past at much higher levels. Currently available genetic toxicity data are also of limited relevance to carcinogenicity in humans due to: 1) the inconsistency with the human cancer studies, 2) human cytogenetic endpoints in peripheral lymphocytes are markers of recent exposure, not past exposure or of biological effect and 3) concerns about confounding effects from human population monitoring studies of small sample sizes. The large body of human data does not indicate that occupational exposure to EO causes increased risk of cancers overall or of brain, stomach or pancreatic cancers. The findings for cancers of the lymphopoietic tissues, specifically leukemia and NHL, are inconclusive. There is limited evidence in males but no indication of an excess risk in females. Additional follow up of these populations is required to clarify these relationships.

Based on sufficient evidence of carcinogenicity in animals, limited evidence in humans and mechanistic data of uncertain relevance, ethylene oxide should be considered a "probable human carcinogen."

3. DOSE-RESPONSE ASSESSMENT—METHODS

3.1. Study Selection

The most critical issue in evaluation of the utility of epidemiological data for dose-response assessment is the quality and completeness of exposure information.[42] Only three of the studies included quantitative exposure estimates that could be linked to individuals.[17,21,22] The most accurate and direct exposure data is from the Hagmar *et al.*[17] study, that included air concentrations and correlations with hemoglobin adducts over the entire period of study observation. Unfortunately, the population was too young and the follow up too short in this study to provide reasonable

Table III. Risk Ratios According to Gender

	Steenland *et al.*		Gardner *et al.*		Hogstedt		Norman *et al.*	
	Men n = 8,214	Women n = 10,040	Manuf. n = 1,471	Hosp. n = 1,405	Men n = 539	Women n = 170	Men n = 204	Women n = 928
All cancer	0.99	0.82	1.14	1.07	1.58	2.12	0.70	1.13
Leukemia	1.16	0.77	2.26	0	6.11	9.09	0	1 obs, 0.4 exp.[b]
Brain cancer	0.86	0.17						
LP[a]-Leukemia	1.81	0.39			1.92	0		
Non-Hodgkin's lymphoma			1.04	0.57			0	0
Female breast cancer		0.85 (42 obs., 50 exp.)						1.7 (12 obs., 7 exp.)

[a] Lymphopoietic.

[b] Ratio not calculated when observed and expected are both less than 2.

confidence that the study is statistically sensitive enough to detect excess cancers of long latency.

Because of their size, length of follow up and available exposure estimates at the individual level, two of the studies (NIOSH and UCC described below) have the requisite attributes to become the basis for dose-response modeling. These studies meet acceptable standards of quality as evaluated by Shore *et al.* in the prior meta-analysis. Their general characteristics are contrasted in Table IV.

The NIOSH study included 18,254 male and female workers employed at least three months at 11 sterilant and three spice plants in the United States.[22] Most of the workers were exposed to EO during sterilization of medical supplies. Workers were followed for an average of 16 years from the time of their first EO exposure through December 31, 1987.

The UCC epidemiological study included 1,896 male workers who were exposed to EO in chemical manufacturing (use and production) and who were followed for an average of 27 years over the period from 1940 to 1988.[20,21] Another 26,965 male workers at the same UCC facilities in the Kanawha Valley of West Virginia, who were not exposed to EO, were followed for an average of 32 years over the same observation period. The EO exposed and unexposed populations were updates of another NIOSH study, a cohort study of UCC workers in the Kanawha Valley.[43]

In the study of UCC manufacturing workers, TWA8 concentrations (ppm) were estimated over four time periods (1925–39, 1940–56, 1957–73 and 1974–78) and three exposure intensity categories (high, medium, low exposure departments). Work history data were complete through 1978, mortality data through 1988. Average exposures in the most recent time period were based on industrial hygiene monitoring conducted at the locations where the study subjects worked. The estimates for the other time periods were inferred from published data on exposure levels in similar manufacturing operations during the time period of interest.[10,44] A separate age-dependent exposure history was developed for each worker based on his department assignments and the estimated exposure levels. The criteria and validation for the department grouping by intensity of exposure is described elsewhere.[20]

Table IV. UCC/NIOSH Study Characteristics

UCC	NIOSH
• n = 1,896	• n = 18,254
• 23% deceased	• 6.4% deceased
• Avg. duration: 5.4 yr.	• Avg. duration: 4.9 yr.
• Avg. follow up: 27.2 yr.	• Avg. follow up: 16.1 yr.
• Avg. first exposed: 1961	• Avg. first exposed: 1970
• Leukemia: 5 observed	• Leukemia: 11 observed
• Lymphoid: 3 observed	• Lymphoid: 19 observed
• Controls: US/other workers	• Controls: US
• Exposure: indirect by decade & intensity	• Exposure: indirect by modeling predictors

The NIOSH study included exposure estimates for jobs that were linked to individuals by job assignment over the study's observation period. More recent direct measurement of EO concentrations and their predictors (size of the sterilizer, product volume, time period) were modeled to estimate historical levels, assuming that they were influenced similarly by these same predictors of exposure. The details of the NIOSH estimation and validation procedures have been described by Griefe *et al.* and Hornung *et al.*[45,46]

3.2. Dose-response Modeling/Added Risk Predictions

The EO cancer dose-response assessment based on the UCC and NIOSH epidemiological datasets explicitly evaluates several different combinations of response, sex, Poisson regression model, latency period, exposure lag periods, and background rates. Leukemia and "lymphoid" response are the two responses of interest based on the overall assessment of the epidemiological and toxicologic literature and both are examined here. The dose-response analyses for the NIOSH data set include sex as a covariate.

The analyses include either no latency or a 10-year latency period. The 10-year alternative assumes that the minimum time between the initiation of exposure and response is 10 years, and disease that occurs prior to 10 years is therefore unrelated to exposure. Two exposure lagging alternatives (no lag, 5 years) are considered in conjunction with the definition of the cumulative dose (ppm-years). Here, lagging means excluding the exposure in the last 5 years immediately preceding an age from that age-specific cumulative dose. Lagging is an attempt to exclude exposure that is deemed irrelevant, because it occurred after the disease process has been initiated.

Poisson regression, a statistical procedure used for the analysis of count data which follows a Poisson distribution,[47–50] is used here to analyze the counts of responses occurring in person-years grouped by age, sex, calendar year, and dose. For grouped data,

it has been shown that the log-likelihood function for the Cox proportional hazards model reduces to that of the Poisson regression model.[50] Callas *et al.* found that both Cox and Poisson procedures were superior to logistic procedures.[51]

In Poisson regression, an individual's hazard rate for a specified response is modeled as the response's background hazard rate multiplied by a rate ratio (RR), which is a function of the individual's age-dependent dose. Specifically,

Mean Response in a Person Year = Background Rate × Effect of Sex × Effect of Age × Effect of Calendar Year × Function (EO dose)

The RR is the ratio of the hazard rate for individuals exposed to the hazard rate of individuals not exposed. Four functional forms of RR as a function of EO dose were used for these analyses.

Linear Model: $RR = 1 + \beta_1 \times (\text{EO dose})$
Power Model: $RR = 1 + \beta_1 \times (\text{EO dose})^{\beta_2}$
Two Polynomial Models: linear and quadratic
$RR = 1 + \beta_1 \times (\text{EO dose}) + \beta_2 \times (\text{EO dose})^2$
linear, quadratic, and cubic
$RR = 1 + \beta_1 \times (\text{EO dose}) + \beta_2 \times (\text{EO dose})^2 + \beta_3 \times (\text{EO dose})^3$

An individual's "EO dose" is the individual's age-dependent cumulative ethylene oxide exposure (ppm-years). Cumulative exposure was grouped into the following ppm years categories: 0, (0–33], (33–125], (125–285], >285. An implicit assumption in this assessment is that dose is proportional (linearly related to) exposure.

Background hazard (mortality) rates are estimated in the Poisson regression modeling in two forms: 1) internally derived for unexposed workers (UCC workers unexposed to EO; estimated from exposed workers by extrapolation to zero exposure for the NIOSH cohort) and 2) from US background rates adjusted for the Healthy Worker Effect.

In Form 1 of the Poisson regression analyses, the background rates are internally derived from the epidemiological data and have the form:

Mean Response Rate in a Person-Year = Background Rate × Effect of Sex × Effect of Age × Effect of Calendar Year × Function (EO dose)

The intervals used to define the strata for the Poisson regression model for age and calendar year are ≤50, (50-70], and >70 years and ≤1939, (1939-1956], (1956-1973], >1973, respectively.

The form of the alternative model (Form 2) that uses the age- and calendar-year specific US mortality rates is given by:

Mean Response Rate in a Person-Year = [Age, Sex and Calendar-Year Dependent U.S. Background Rate × Healthy Worker Effect] + [Age, Sex and Calendar-Year Dependent U.S. Background Rate × Function (EO dose)].

For Form 2 of the Poisson regression model, the partitions for the different strata were constrained to the categories available from the Vital Statistics of the United States, i.e., 5-year age groups and 10-year calendar periods.

For both Forms 1 and 2, the parameters (β_1, β_2, β_3) in the four different RR models are estimated from the epidemiological data and then used to compute lifetime added risk.

For *future occupational exposures,* the added cancer risks are estimated from the Poisson regression model (Form 1 or 2) using the relationship:

Mean Response Rate in a Person Year = [Background Rate × Effect of Sex × Effect of Age × Effect of *Most Recent* Calendar Year] × Function (EO Dose),

where the effect of the most recent calendar year is conservatively used assuming that the effect of exposures in the last calendar year interval in the study are going to prevail in the future. The added risk calculation also incorporates competing risks.

For *future environmental exposures* (continuous exposure for 70 years), the added cancer risk computations are estimated from the Poisson regression model using the relationship:

Mean Response Rate in a Person Year = [1990 U.S. Age-Dependent Population Background Rates] × Function (EO Dose)

The 1990 U.S. population age-dependent competing risks are incorporated in the computations of added risks.[52]

If a worker inhales $10m^3$ over an eight-hour shift and works 240 days per year, then inhalation of $18m^3$ per day for 365 days per year would make 1 ppm-year of environmental exposure equal approximately to 2.74 ppm-years of occupational exposure. This equivalence is used herein.

3.3. Point of Departure Analyses

The proposed revisions to the EPA carcinogen risk assessment guidelines include the use of POD

approaches and margins of exposure (MOEs) in cancer risk assessment. A POD is the dose needed to attain a specified additional cancer risk. For example, the POD, ED_{10}, is the effective dose required to reach an added risk of 10%.

For animal bioassay data, the POD for a 10% increase in the risk over the background is often used because an additional response of 10% frequently occurs within the range of experimental dose levels. However, for epidemiological data, no clear guidelines are available. In epidemiological studies, where individuals are subject to doses much lower than the doses applied to experimental animals, the response rates are much lower.

Reference increases in risks for epidemiological studies should be such that the effective dose predicted from several different models are relatively invariant and such that the size of the effective dose is reasonably within the dose range observed. This is the procedure adopted for these analyses of leukemia in relation to environmental exposures, using both the UCC and NIOSH data and Form 1 of the Poisson regression model. From the POD, results are shown for a variety of MOEs.

4. DOSE-RESPONSE ASSESSMENT—RESULTS

4.1. Dose-Response Models

Analyses for all possible combinations of the alternatives described above were evaluated. The estimated parameters for the functions of EO dose in the fitted models are not notably different when the Poisson regression estimates the background rates from the epidemiological study data (Form 1) or uses mortality rates from the general U.S. population (Form 2). Latency and lagging of dose also do not appreciably affect the fitted models. For example, the fitted model predictions of the leukemia rate ratios, for the case in which there are no latency and no lag, are shown in Fig. 2 and for the case in which the latency is 10 years and doses are lagged 5 years, are shown in Fig. 3. The dots are the nonparametric estimates of the rate ratios based on the UCC study data. Although the nonparametric estimates in Figs. 2 and 3 differ in the low-dose region, the fitted models are not appreciably different. (Note that since the NIOSH study did not include internal controls, nonparametric estimates cannot be presented.) The models that best fit the data according to the maximum likelihood estimation procedure are also apparent from the results given in Figs. 2 and 3. Although none of the models fit the data statistically significantly better than the background risk model (i.e., no dose-dependent change and zero added risk), the improvement in the likelihood for the polynomial and power models over the likelihood for the linear model is at least as large as the improvement in the likelihood for the linear model over the likelihood of the background risk model.

For leukemia, the fitted models for the UCC data are very similar to the corresponding fitted models for the NIOSH data. Figures 4 to 6 show results for the four leukemia models using the UCC and NIOSH databases when only the person years after 10 years from first exposure are included and the dose is lagged for 5 years.

4.2. Added Risk Values, Environmental Exposures: Leukemia

The predicted added risks for environmental exposures to 1 ppb of EO in the air for 24 hours a day, 7 days a week, during 70 years are presented in Tables V and VI. The 32 values of the added risks for leukemia provide an indication of the influence of the following choices: 1) the function of EO dose, 2) dataset, 3) latency period, 4) lag period and 5) background hazard rate.

Table V gives the added risks for Form 1 in which the Poisson regression estimates the background rate from the epidemiological data and computes the added risks using the 1990 U.S. population background rates and competing risks. There is no appreciable difference between the added risk predictions when no latency and no lag are assumed and the added risk predictions estimated with the assumption of a 10-year latency and 5-year lag. As expected, the similarity of the leukemia dose-response models using the UCC and NIOSH data are reflected in the consistency of the added risk values. The predicted added risks estimated from the two datasets are remarkably similar. There are greater differences among the added risks for the different forms of the function of dose than the differences caused by either the choice of data set or the assumptions about latency and lag. For environmental exposures to 1 ppb EO, using the nonlinear models, the predicted added risks of leukemia are orders of magnitude lower than

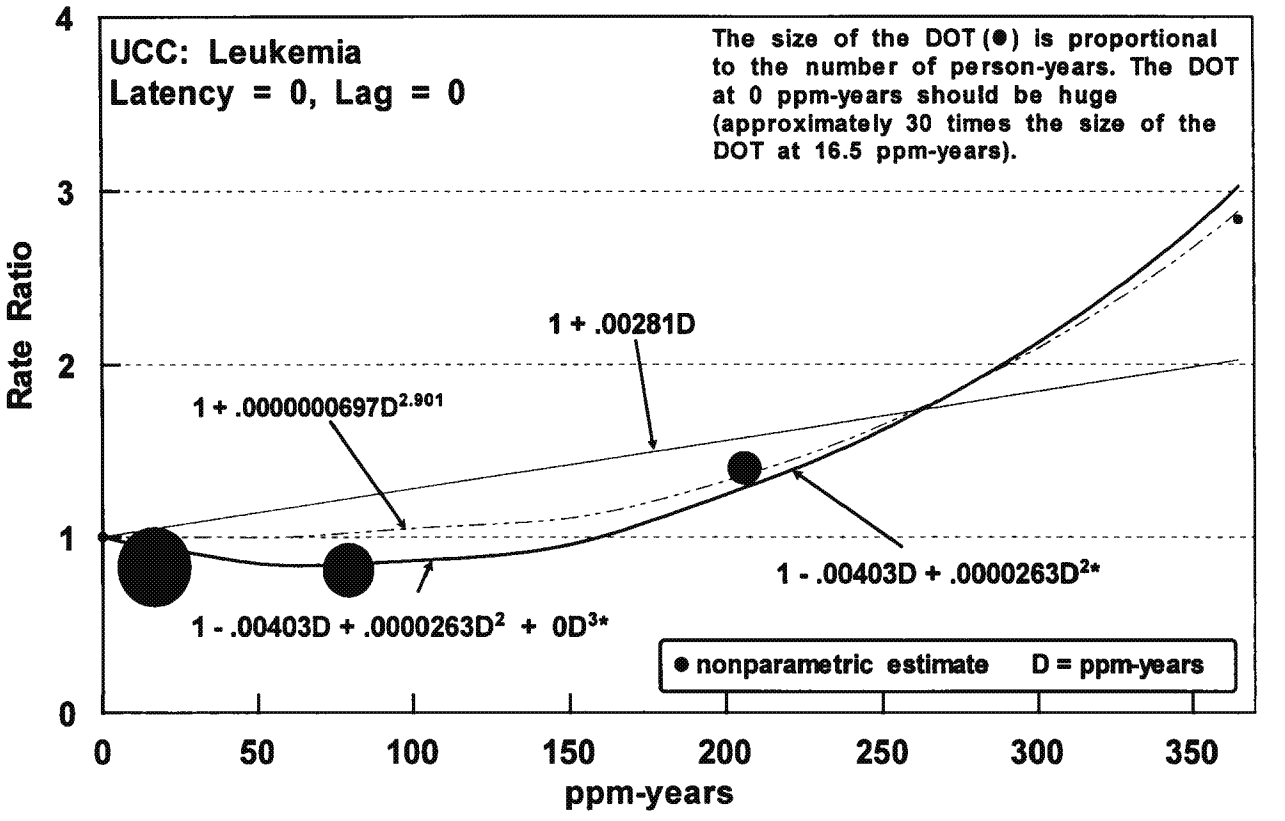


Fig. 2. Fitted and nonparametric estimates of the leukemia rate ratios for the UCC epidemiological data set and internally derived background rates with no latency and no lag.

1×10^{-6}. The linear model yields the highest added risks of approximately 1×10^{-6}.

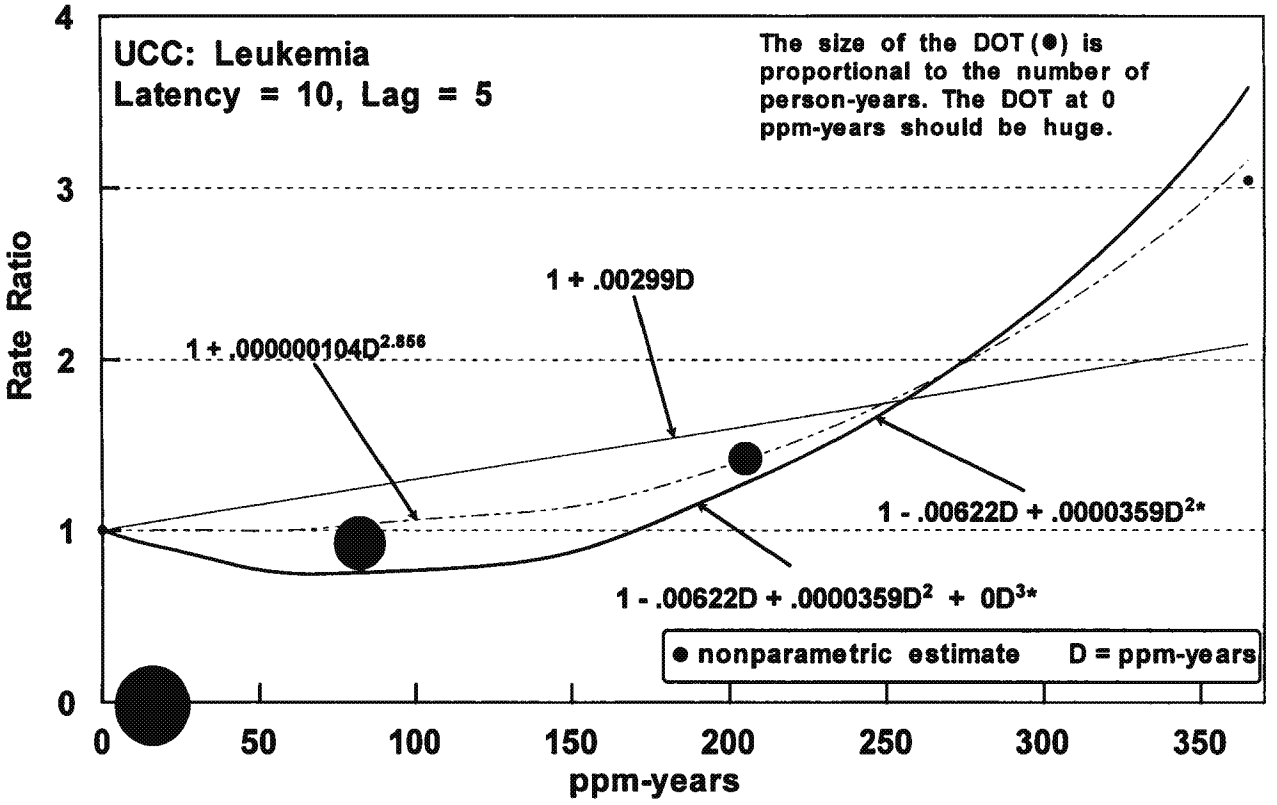
The robustness of all the estimates were evaluated by computing the added risks with alternative dose partitions every 20 ppm-years, alternative calendar-years every five years and alternative age groups every five years. The results were not notably different. For example, for leukemia in the UCC study with no lag or latency, the added risks were 9.5×10^{-13}, 2.9×10^{-12}, 1.2×10^{-12}, and 6.3×10^{-13} for the power model and the original partitions, the alternative dose partitions, the alternative calendar-year partitions, and the alternative age partitions, respectively (1.2×10^{-6}, 1.1×10^{-6}, 1.2×10^{-6}, and 1.4×10^{-6} for the linear model).

The estimated added risks of leukemia from the UCC study are small, regardless of whether the Kanawha Valley unexposed workers are used, or when no controls are used and the added risks are computed from the background rates extrapolated from the workers exposed to EO.

Table VI shows the predicted added leukemia risks for the alternate Poisson regression (Form 2) using U.S. population background rates. As with Form 1 of the Poisson regression, although the polynomial and power models fit the data best and result in lower added risks, none of the models fit the data statistically significantly better than just the background model. Similar to Table V, the predicted added risks of leukemia for environmental exposures to 1 ppb for 70 years range from 0 to approximately 1×10^{-6}.

4.3. Added Risk Values, Environmental Exposures: "Lymphoid" Tumors

The analyses of the NIOSH dataset by Stayner *et al.*[40] observed the strongest effect for the category



*The second and third degree polynomial models are the same because the coefficient of the cubic term is zero.

Fig. 3. Fitted and nonparametric estimates of the leukemia rate ratios for the UCC epidemiological data and internally derived background rates with 10 latency and 5 yr. lag.

of cancers he referred to as "lymphoid" tumors, a grouping of lymphocyctic leukemia and NHL. The UCC epidemiological data set was, therefore, examined for this response. A deficit was observed when compared to the unexposed UCC workers and when compared to the general U.S. population. There were no leukemia death certificates in the UCC study specified as lymphocytic, a nonsurprising finding since histologic type is often not recorded on death certificates. Figures 7 and 8 show the fitted Poisson regression models (Form 1) and the non-parametric estimates of the UCC data set for two different assumptions of latency and lag. A clear inverse relationship between ppm years and the "lymphoid" response is evident using the UCC data. In contrast with leukemia, the fitted models for "lymphoid" response in the UCC and NIOSH data are noticeably different. While the UCC data suggest a decrease in risk ratios as cumulative dose increases, the fitted models for the NIOSH data (not shown) suggest an increase in the risk ratios as cumulative dose increases. The predicted risks are also different (Tables VII and VIII). While the predicted added risks for environmental exposures from the UCC data are zero, the predicted added risks from the NIOSH data set are approximately 1×10^{-5} or less for the lymphoid response for all of the same combinations of latency periods, lags, and Poisson regression models that were examined for leukemia.

4.4. Added Risk Values, Occupational Exposures

The predicted added leukemia risks at age 70 for occupational exposure to 1 ppm of EO in the air for 8 hours a day, 5 days a week, during a working lifetime of 45 years are presented in Table IX. The range of risk predictions using Form 2 (not shown)

is not notably different. The predicted added "lymphoid" tumor risks for occupational exposure using the UCC dataset are 0, irrespective of the form of the Poisson regression used. The NIOSH-based risks using Form 1 are in the 10^{-4} region for the nonlinear models, and is 1×10^{-3} for the linear model with a 10-year latency and 5-year lag (Table X). The added risks using the NIOSH dataset and Form 2 (not shown) are within this same range.

4.5. Point of Departure Analyses

POD doses are computed using the Poisson regression model (Form 1) with internally derived estimates of background. The POD for 0.1%, 0.5%, 1% and 10% increase over the background probability of leukemia (ED_{001}, ED_{005}, ED_{01}, ED_{10}, respectively) are shown in Tables XI and XII for the UCC and NIOSH data, respectively, assuming a 10-year latency and 5-year lag in dose. The ED_{001}'s are the most consistent predictions across models (or at least the lowest among equally consistent predictions) and, therefore, are a robust predictor for the POD. Furthermore, the doses at 0.1% additional risk over the background are environmental exposures to approximately 1 ppm for 70 years, which is equivalent to about 190 ppm-years in an occupational setting for 45 years; and the dose of 190 ppm-years is about the middle of the range of exposures for which the shape of the dose-response relationship is reasonably clear in the UCC and NIOSH data sets.

The PODs for leukemia based on the UCC data are very similar to those based on the NIOSH data set. The average of the ED_{001} values for environmental exposures for 70 years for the different models and the UCC and NIOSH data sets is approximately 1.3 ppm.

Based on the ED_{001} of 1.3 ppm or 1,300 ppb, the environmental concentration of EO corresponding to a specific MOE can be computed by dividing the benchmark dose by a specified margin of exposure.

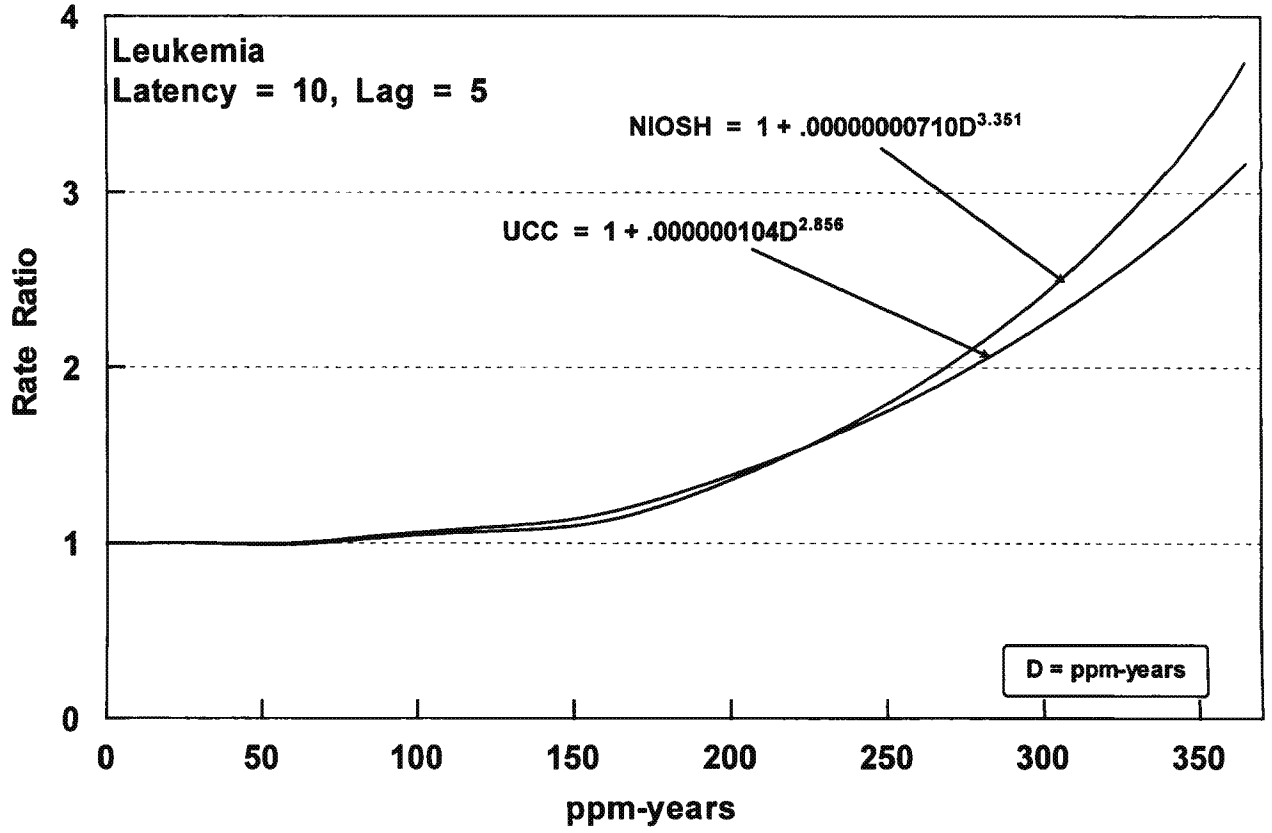


Fig. 4. Fitted power model estimates of the leukemia rate ratios for the UCC and NIOSH epidemiological data and internally derived background rates.

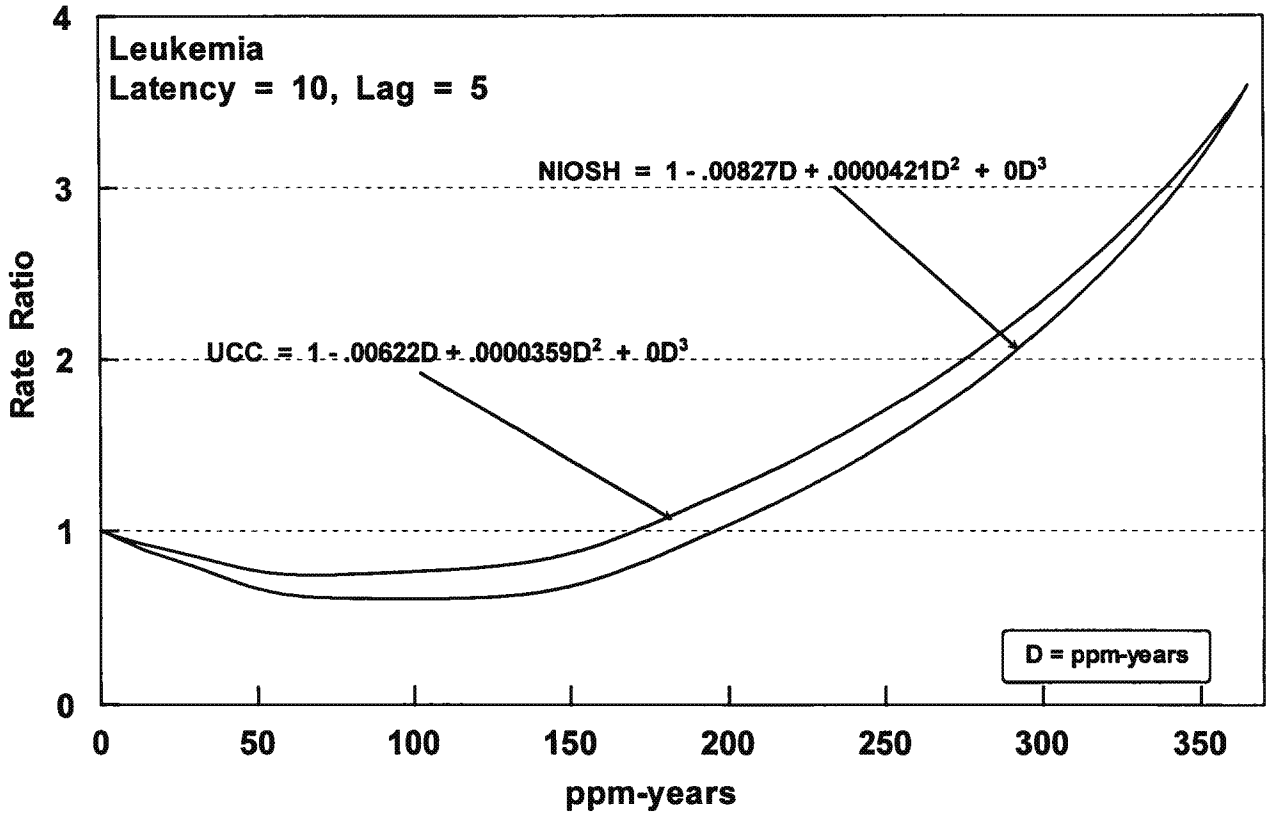


Fig. 5. Fitted polynomial model (linear, quadratic and cubic model and equivalent linear and quadratic model) estimates of the leukemia rate ratios for the UCC and NIOSH epidemiological data and internally derived background rates.

For example, for a margin of exposure of 10, the corresponding concentration of EO in air is 130 ppb, while an MOE of 1000 corresponds to 1.3 ppb (i.e., equivalent to a 1×10^{-6} added risk with an assumption of linearity).

5. COMPARISONS WITH PRIOR RODENT-BASED ADDED CANCER RISK PREDICTION

The Snellings *et al.*[3] chronic bioassay is recognized as establishing the animal carcinogenicity of EO. OSHA's 1983 risk assessment was based on total number of malignant tumors in this study for male rats and, separately, for female rats, using the linearized multistage and one hit models.[8] Interspecies dose extrapolation was based on mg/kg/body weight. OSHA's risk assessment predicted excess lifetime cancer risks that ranged from 2.1 to 3.3 per 1,000 workers from exposure to EO at 1 ppm. EPA's quantitative risk assessment[9] also used the Snellings *et al.* chronic bioassay. Dose was assumed to be equivalent between species on the basis of mg/surface area. An upper bound risk estimate was calculated using the linearized multistage model. Based on mononuclear cell leukemias and brain gliomas in female rats, EPA estimated an upper-limit incremental unit (1 ppm) risk estimate of 1.9×10^{-1}. For 1 ppb lifetime environmental exposure, this converts to 1.9×10^{-4}.

Table XIII presents the added risk predictions from the prior OSHA and EPA risk assessments based on animal bioassay data and upper bound procedures and the added risk estimates from the UCC and NIOSH epidemiological data. For comparison purposes, the OSHA occupational added risk prediction has been converted to the equivalent 1 ppb environmental prediction (2.4×10^{-5}) and the EPA environmental added risk prediction has been converted to the equivalent 1 ppm occupational prediction (2.6×10^{-2}). A range of epidemiology-based estimates is presented to reflect the four different RR models and two different datasets, two combinations of latency and exposure lag. For simplicity, only risk

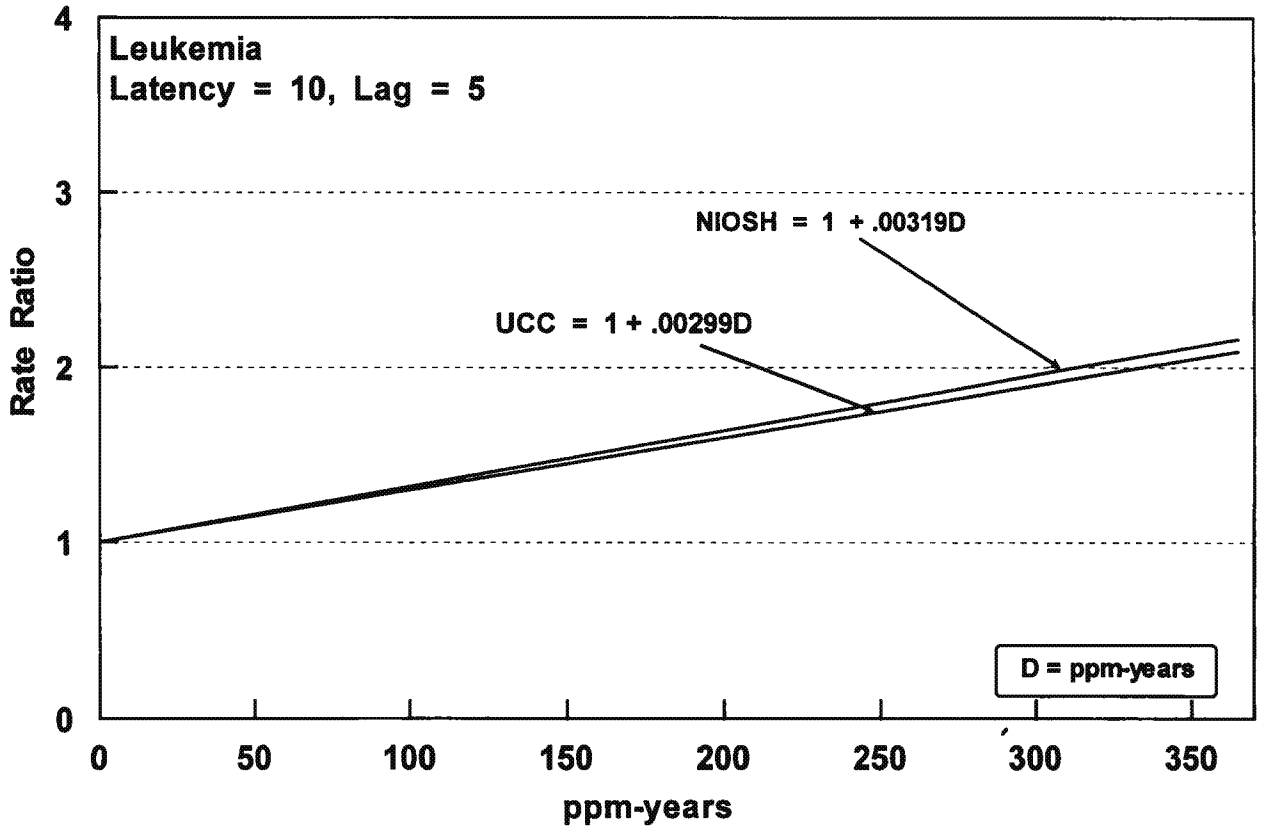


Fig. 6. Fitted linear model estimates of the leukemia rate ratios for the UCC and NIOSH epidemiological data and internally derived background rates.

estimates using internally derived background rates are presented.

Although based on the same rat dataset, the EPA predictions are about an order of magnitude higher than OSHAs. This can be explained by different assumptions related to target organ and interspecies extrapolation. When the results based on human data are compared to the prior rodent-based risk assessments, a clear reduction in added risk predictions is observed. The reduction is due, not only to

Table V. Leukemia Added Cancer Risk Predictions[a] for Environmental Exposure to 1 ppb for 70 Years Using Form 1[b] of Poisson Regression Model

Model: function of cumulative exposure	Latency = 0 years Lag = 0 years		Latency = 10 years Lag = 5 years	
	UCC Data	NIOSH Data	UCC Data	NIOSH Data
Power	9.5×10^{-13}	1.7×10^{-13}	1.2×10^{-12}	3.3×10^{-14}
Polynomial: linear & quadratic & cubic	0.0[c]	0.0	0.0	0.0
Polynomial: linear & quadratic	0.0	0.0	0.0	0.0
Linear	1.2×10^{-6}	1.1×10^{-6}	1.2×10^{-6}	1.2×10^{-6}

[a] Uses 1990 U.S. age-specific leukemia mortality rates and competing risks.
[b] Leukemia background rates estimated from study data (UCC unexposed workers for UCC study, extrapolated from exposed population for NIOSH study).
[c] 0.0 indicates that the estimated added cancer risk is zero or negative.

Table VI. Leukemia Added Cancer Risk Predictions[a] for Environmental Exposure to 1 ppb for 70 Years Using Form 2[b] of Poisson Regression Model

Model: function of cumulative exposure	Latency = 0 years Lag = 0 years		Latency = 10 years Lag = 5 years	
	UCC Data	NIOSH Data	UCC Data	NIOSH Data
Power	1.5×10^{-10}	3.5×10^{-15}	1.0×10^{-6}	1.3×10^{-15}
Polynomial: linear & quadratic & cubic	0.0[c]	0.0	2.9×10^{-6}	0.0
Polynomial: linear & quadratic	0.0	0.0	2.9×10^{-6}	0.0
Linear	1.9×10^{-6}	6.5×10^{-7}	3.1×10^{-6}	9.0×10^{-7}

[a] Uses 1990 U.S. age-specific leukemia mortality rates and competing risks.
[b] Uses age- and calendar-year specific U.S. leukemia mortality rates and adjusts for healthy worker effect.
[c] 0.0 indicates that the estimated added cancer risk is zero or negative.

the data, but also to the methodology and departures from default assumptions that are not necessary with human data. Using the three nonlinear models, the leukemia estimates based on epidemiological data are many orders of magnitude less than 1×10^{-6} (including zero risk) at 1 ppb lifetime exposure and on the order of 1×10^{-6} using the linear model. The added leukemia risks for occupational exposures of 1 ppm range from zero risk to a maximum of 2×10^{-4}. Furthermore, the leukemia results are remarkably similar irrespective of the dataset used.

The dose-response assessment based on the

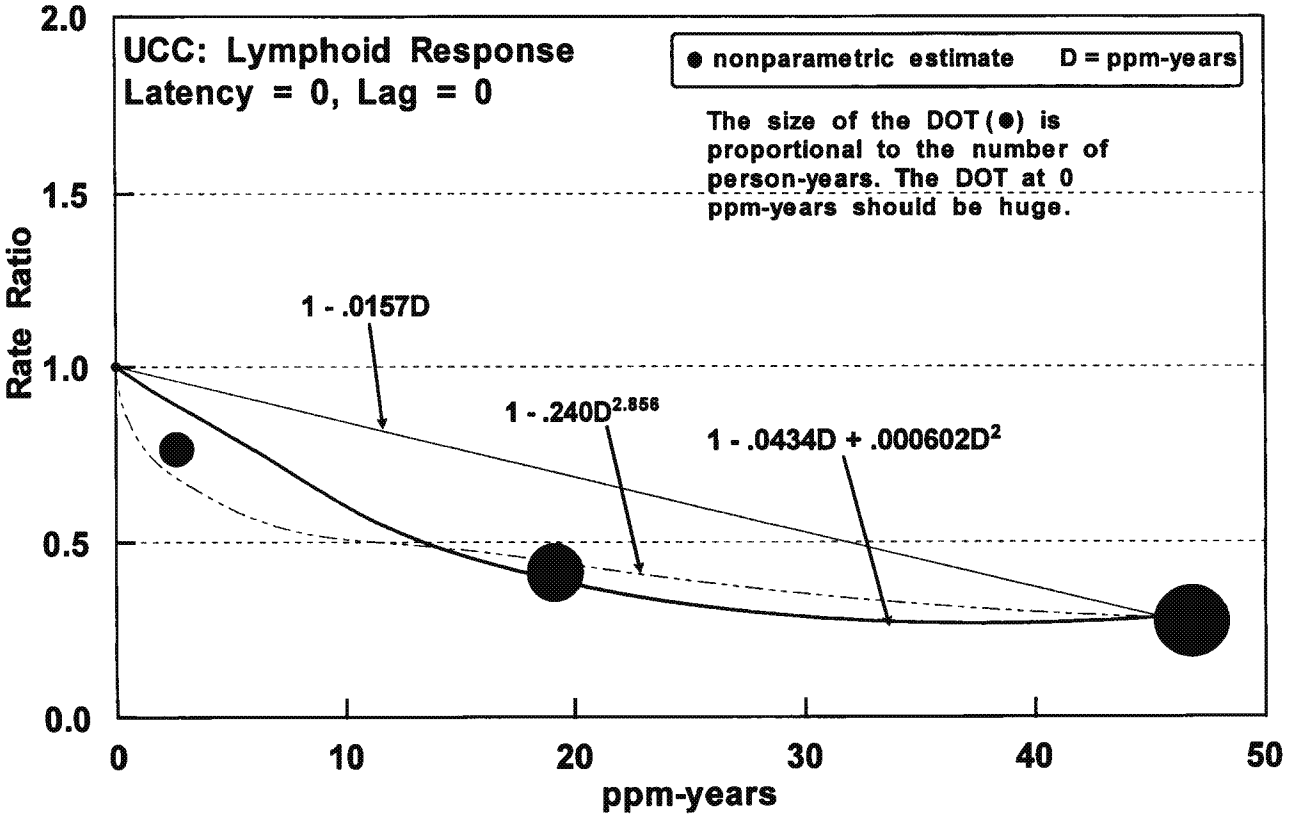


Fig. 7. Fitted and nonparametric estimates of the lymphoid response rate ratio for the UCC epidemiological data and internally derived background rates.

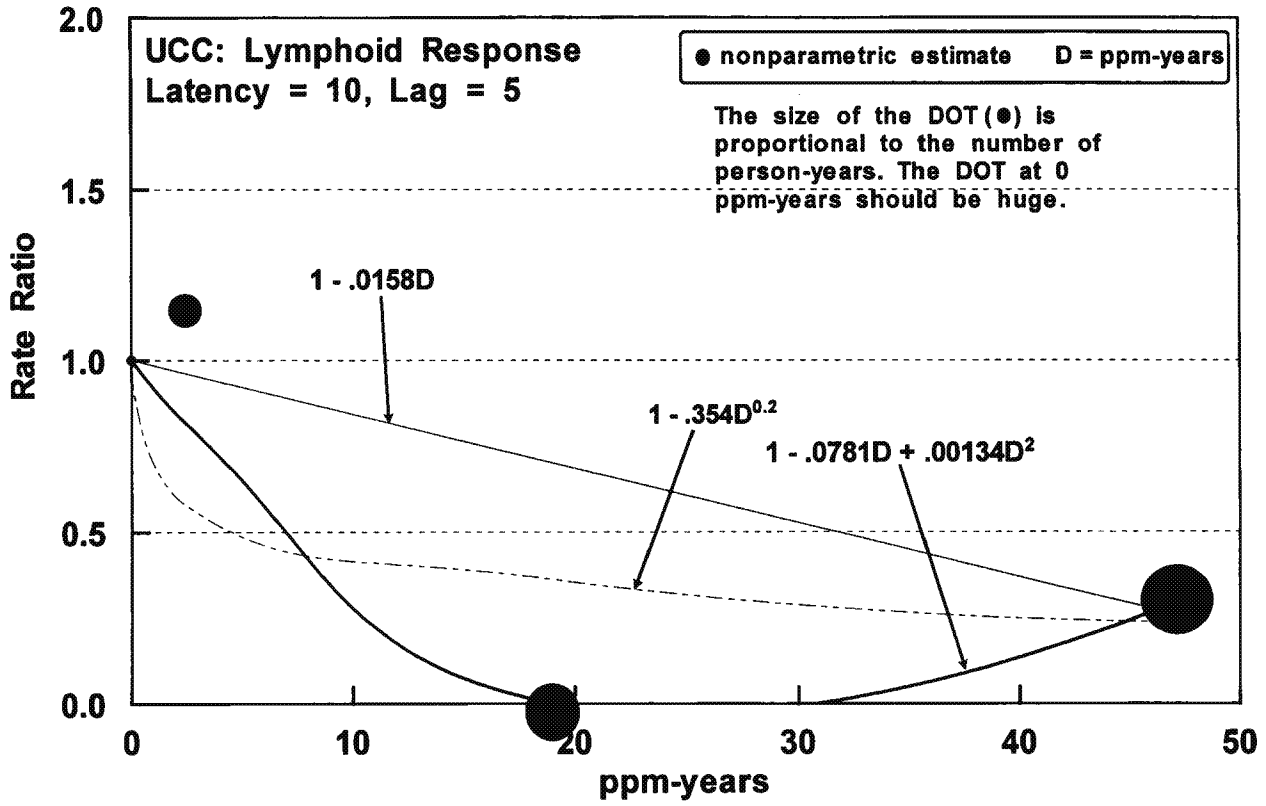


Fig. 8. Fitted and nonparametric estimates of the lymphoid response rate ratios for the UCC epidemiological data and internally derived background rates.

"lymphoid" response produced extremely different results, depending on choice of dataset. The UCC data showed a deficit of this cause of death, resulting in added risk predictions of zero for both occupational and environmental exposures, while the maximum prediction of added risk based on the NIOSH data is 1.8×10^{-5} at 1 ppb lifetime exposure and 1×10^{-3} at 1 ppm occupational exposure. (The results from the Cox proportional hazards analysis for "lymphoid" tumors in the Stayner *et al.* paper would predict an added risk of 2.35×10^{-6} for 1 ppb lifetime exposure.[40])

Table VII. Lymphoid Added Cancer Risk Predictions[a] for Environmental Exposure to 1 ppb for 70 Years Using Form 1[b] of Poisson Regression Model

Model: function of cumulative exposure	Latency = 0 years Lag = 0 years		Latency = 10 years Lag = 5 years	
	UCC Data	NIOSH Data	UCC Data	NIOSH Data
Power	0.0[c]	1.6×10^{-7}	0.0	7.7×10^{-6}
Polynomial: linear & quadratic & cubic	0.0	2.9×10^{-6}	0.0	1.4×10^{-5}
Polynomial: linear & quadratic	0.0	2.9×10^{-6}	0.0	1.4×10^{-5}
Linear	0.0	7.8×10^{-6}	0.0	1.8×10^{-5}

[a] Uses 1990 U.S. age-specific lymphoid mortality rates and competing risks.
[b] Lymphoid background rates estimated from study data (UCC unexposed workers for UCC study, extrapolated from exposed population for NIOSH study).
[c] 0.0 indicates that the estimated added cancer risk is zero or negative.

Table VIII. Lymphoid Added Cancer Risk Predictions[a] for Environmental Exposure to 1 ppb for 70 Years Using Form 2[b] of Poisson Regression Model

Model: function of cumulative exposure	Latency = 0 years Lag = 0 years		Latency = 10 years Lag = 5 years	
	UCC Data	NIOSH Data	UCC Data	NIOSH Data
Power	0.0[c]	4.6×10^{-8}	0.0	1.1×10^{-6}
Polynomial: linear & quadratic & cubic	0.0	1.3×10^{-6}	0.0	5.4×10^{-6}
Polynomial: linear & quadratic	0.0	1.3×10^{-6}	0.0	5.4×10^{-6}
Linear	0.0	6.6×10^{-6}	0.0	8.8×10^{-6}

[a] Uses 1990 U.S. age-specific lymphoid mortality rates and competing risks.
[b] Uses age- and calendar-year specific U.S. lymphoid mortality rates and adjusts for healthy worker effect.
[c] 0.0 indicates that the estimated added cancer risk is zero or negative.

6. DISCUSSION

Much scientific data has accumulated that reduces uncertainties that remained in the rodent-based regulatory risk assessments of the 1980s. The value of having 10 independent epidemiology studies is the ability to assess the external consistency of findings with those from individual human studies and animal bioassays. The human evidence, in its totality, does not indicate EO causes specific types of cancers (brain, stomach, pancreas) for which concerns have been raised in the past, based on isolated human or rodent studies. The meta-analysis and tests of heterogeneity provide compelling evidence that the putative high risk for leukemia based on the early Hogstedt reports was an incorrect inference. Several studies of worker populations using or producing EO during the infancy of the chemical industry and with extensive follow up show no increase in leukemia. There is evidence, however, from both animal and human studies to suggest that cancers of the lymphopoietic tissues (leukemia, NHL) warrant additional epidemiological follow up.

The meta-analysis used expected values reported in the published papers that were derived from general population mortality rates. Such comparisons may give rise to concerns about the healthy worker effect (HWE), i.e., more favorable mortality among the employed compared to persons in the general population, particularly for noncancer causes of death in cohort studies with short follow-up periods.[53] The HWE diminishes with length of follow up and is thought to have little impact on cancer mortality comparisons, however, particularly in studies with reasonable observation periods, such as the UCC and NIOSH investigations.[54–56] The results of studies with relatively short follow up, such as the Hagmar *et al.*[17] study, should be interpreted more

Table IX. Leukemia Added Cancer Risk Predictions at Age 70[a] for Occupational Exposure to 1 ppm for 45 Years (Age 20 to 65) Using Form 1[b] of Poisson Regression Model

Model: function of cumulative exposure	Latency = 0 years Lag = 0 years		Latency = 10 years Lag = 5 years	
	UCC Data	NIOSH Data	UCC Data	NIOSH Data
Power	5.5×10^{-6}	2.3×10^{-6}	5.2×10^{-6}	1.6×10^{-6}
Polynomial: linear & quadratic & cubic	0.0[c]	0.0	0.0	0.0
polynomial: linear & quadratic	0.0	0.0	0.0	0.0
Linear	2.2×10^{-4}	1.1×10^{-4}	2.0×10^{-4}	1.7×10^{-4}

[a] Uses estimated worker leukemia background rate and 1990 U.S. age-specific competing risks.
[b] Leukemia background rates estimated from study data (UCC unexposed workers for UCC study, extrapolated from exposed population for NIOSH study).
[c] 0.0 indicates that the estimated added cancer risk is zero or negative.

cautiously. An important advantage of the meta-analysis is that studies with short latencies and, therefore, fewer deaths, make little contribution to the overall results. In addition, the methodology used in the present meta-analysis does not rely only on overall results but also examines the entire set of data by latency periods.

In the UCC study, there were no new hires included in the exposed and unexposed cohorts after 1978, reducing the proportion of active employees and thereby the potential for a HWE. The UCC study has the added advantage of observing similar results when comparisons were made to a working population from the same facilities as the exposed group, removing concerns about the HWE and risk factors related to the geographic region that may not exist in the general population.

With respect to deriving risk estimates for the dose-response analyses, several approaches were taken to attenuate concerns about the HWE and inappropriate comparison groups: 1) three alternative methods were used to estimate background hazard rates (general population with an adjustment for the HWE, unexposed workers, internally derived from the exposed cohorts) and 2) comparisons were presented using various alternative exposure lagging and latency criteria, both of which have been recommended to address the HWE.[56,57]

The present EO carcinogenicity assessment and that of IARC (1984) are in agreement that the epidemiological evidence is "limited". This hazard characterization, however, differs from that of IARC, who placed EO in category 1, based on different interpretations of genetic toxicity data in humans. Additional EO genetic toxicity studies and a clearer understanding of their implications have evolved over the past few years, raising further concerns about the relevance for predicting carcinogenicity. No studies have demonstrated a direct relationship between cancer in humans and exposure indicators, such as SCEs, chromosomal aberration and hemoglobin adduct formation. Recent data show that the DNA damage that could lead to mutations will repair even in workers who were highly exposed to EO.[32] Furthermore, the workers in the large body of epidemiology studies were exposed at levels that far exceed those reported to be showing genotoxic effects in humans,[58,59] and the evidence of carcinogenicity remains limited after extensive follow up. The limitations of EO genotoxicity data, particularly data derived from studies in humans, have been addressed in greater detail by Preston.[36]

The rich EO data also permit application of the major modifications to EPAs cancer guidelines. These include the principles of greater weight to high quality human data, a weight of the evidence approach to hazard, the inclusion of a hazard narrative, a point of departure approach to dose-response, consideration of plausible alternatives and presentation of a range of risk estimates to address uncertainties. The modeling of dose-response and lifetime added risk incorporated the key explanatory factors and their modifiers that are characteristic of epidemiological data—e.g., several approaches to estimation of background hazard rates, sex, age-dependent and lagged exposures, time since first exposure, the healthy worker effect and competing risks.

The epidemiologically-based added risk predictions are generally many orders of magnitude lower than those based on the rodent chronic bioassays.

Table X. Lymphoid Added Cancer Risk at Age 70[a] for Occupational Exposure to 1 ppm for 45 Years (Age 20 to 65) Using Form 1[b] of Poisson Regression Model

Model: function of cumulative exposure	Latency = 0 years Lag = 0 years		Latency = 10 years Lag = 5 years	
	UCC Data	NIOSH Data	UCC Data	NIOSH Data
Power	0.0[c]	2.8×10^{-4}	0.0	8.1×10^{-4}
Polynomial: linear & quadratic & cubic	0.0	3.6×10^{-4}	0.0	8.5×10^{-4}
Polynomial: linear & quadratic	0.0	3.6×10^{-4}	0.0	8.5×10^{-4}
Linear	0.0	7.1×10^{-4}	0.0	1.0×10^{-3}

[a] Uses estimated worker leukemia background rate and 1990 U.S. age-specific competing risks.
[b] Lymphoid background rates estimated from study data (UCC unexposed workers for UCC study, extrapolated from exposed population for NIOSH study).
[c] 0.0 indicates that the estimated added cancer risk is zero or negative.

Table XI. Point of Departure[a] for Leukemia and Environmental Exposures to Ethylene Oxide for 70 Years Using Form 1[b] of Poisson Regression Model and Assuming a 10-year Latency Period and a 5-year Lag in Dose Based on the UCC Data

Model: function of cumulative exposure	Environmental concentration in ppm			
	ED_{001}	ED_{005}	ED_{01}	ED_{10}
Power	1.32	2.34	2.98	6.82
Polynomial: linear & quadratic & cubic	1.46	2.22	2.85	7.79
Polynomial: linear & quadratic	1.46	2.22	2.85	7.79
Linear	0.87	4.36	8.74	92.72

[a] Uses 1990 U.S. age-specific leukemia mortality rates and competing risks.
[b] Leukemia background rates estimated from UCC unexposed workers.

For leukemia, all scenarios examined with the human data produced lower added risk predictions. For the "lymphoid" response (lymphocytic leukemia and NHL combined), the UCC data predicted no added risk, while the NIOSH predictions were in the range of 10^{-7} to 10^{-5} at 1 ppb environmental exposures and 10^{-4} to 10^{-3} at 1 ppm occupational exposures. In addition to the extreme inconsistency between the two studies, there is much greater uncertainty about the accuracy and completeness of the response data. Such discrepancies between the two studies are not unexpected, given the inaccuracy and incompleteness of histologic data on death certificates. For example three of the 11 leukemia deaths (27%) were unspecified as to histologic type on the death certificates and, therefore, excluded from the NIOSH "lymphoid" analysis because of missing data.

7. CONCLUSIONS

EPA's revised cancer guidelines recommend preference for quality human data, a hazard characterization narrative, a dose-response assessment that includes mathematical modeling and POD approach, use of mode of action to inform the shape of the curve in the low-dose region and consideration of plausible alternatives. We have attempted to apply these concepts to a hazard characterization and dose-response assessment for EO, a chemical for which there exists a large body of scientific data derived from both animals and humans. Application of EPAs revised regulatory guidelines to an EO cancer risk assessment based on epidemiological data considerably modifies scientific understanding of the hazard potential of this chemical and provides added risk estimates that are several fold less than animal-based predictions.

ACKNOWLEDGMENTS

This work would not have been possible without the cooperation of NIOSH who provided their data to us. We also benefited from the publications, experience and helpful technical comments provided by

Table XII. Point of Departure[a] for Leukemia and Environmental Exposures to Ethylene Oxide for 70 Years Using Form 1[b] of Poisson Regression Model and Assuming a 10-year Latency Period and a 5-year Lag in Dose Based on the NIOSH Data

Model: function of cumulative exposure	Environmental concentration in ppm			
	ED_{001}	ED_{005}	ED_{01}	ED_{10}
Power	1.35	2.18	2.68	5.42
Polynomial: linear & quadratic & cubic	1.58	2.25	2.81	7.35
Polynomial: linear & quadratic	1.58	2.25	2.81	7.35
Linear	0.81	4.09	8.20	86.78

[a] Uses 1990 U.S. age-specific leukemia mortality rates and competing risks.
[b] Leukemia background rates estimated from exposed workers.

Table XIII. Comparison of Upper Bounds on the Added Risk Based on Animal Data and the Estimated Added Risks Based on Epidemiological Data

Source of risk estimate	Occupational exposure to 1 ppm[a]	Environmental exposure to 1 ppb[b]
EPA 1985	2.6×10^{-2}[c]	1.9×10^{-4}
OSHA 1983	2.1×10^{-3} to 3.3×10^{-3}	1.6×10^{-5} to 2.4×10^{-5}[c]
Epidemiological data leukemia[d]	0 to 2.2×10^{-4}	0 to 1.2×10^{-6}
Epidemiological data lymphoid response[d]	0 to 1.0×10^{-3}	0 to 1.8×10^{-5}

[a] Predicted risk by age 70 given working lifetime (45 years) exposure.
[b] Predicted risk by age 70 given lifetime exposure.
[c] Using a 70-year lifetime and OSHA's (1983) assumption that a lifetime occupational exposure is 8 hours per day, 5 days per week, 46 weeks per year, for 45 years in a 54-year lifespace since initial exposure.
[d] Form 1 of Poisson regression model.

Dr. Leslie Stayner of NIOSH on the use of epidemiology data in dose-response assessment. The authors also acknowledge the contribution of Dr. Julian Preston of EPA, formerly of CIIT (Chemical Industry Institute of Toxicology), for his review of the genotoxicology portions of this paper. The work of Drs. Sielken and Valdez-Flores was supported by the Ethylene Oxide Industry Panel of the Chemical Manufacturers Association.

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